REMARKS

Applicant has amended claim 1 to correct a typographical error. This amendment is clerical in nature; therefore, it introduces no new matter, and its entry is respectfully requested. Applicant has also rewritten claim 15 in independent form. This amendment is editorial in nature. Therefore, it introduces no new matter, and its entry is respectfully requested.

Applicant appreciates the Examiner's indication that claim 15 was free of prior art. Applicant also appreciate the Examiner's withdrawal of the rejection of claims 1-7 pursuant to 35 U.S.C. §112, first paragraph.

Claims 1-7 were rejected under 35 U.S.C. §103(a) as being unpatentable over Vassallo et al., Mayo Clinic Proceedings.

Applicant respectfully submits that this rejection should be withdrawn for the following reasons.

As the Examiner acknowledges, theophylline is not a type IV specific PDE4 inhibitor. Rather, theophylline is explicitly described as a non-selective PDE inhibitor at page 347, third full paragraph, lines 26-27, of Vassallo et al. Indeed, at page 347, after discussing the various known PDE family, i.e., PDE I to VII, Vassallo et al. concludes that inhibition of PDEs in inflammatory cells results in a wide range of immunomodulatory effects. Vassallo et al. further indicates that in some allergic diseases and in the asthmatic airways the expression of PDEs generally may be increased and concludes:

> Thus, the nonselective PDE inhibitor theophylline may have a greater than expected inhibitory effect on PDEs in the airways of patients with asthma than in those with normal airways.

In that same paragraph, Vassallo et al. goes on to conjecture that there may also be other PDEs that have not yet been discovered that are sensitive to inhibition from theophylline. At page 348, it is pointed out that there are differences between specific PDE4 inhibitors and the nonselective PDE inhibitor, theophylline. Specifically, a distinction is made between theophylline and the prototypical PDE type IV inhibitor, rolipram, at page 348. Therein, it is taught:

> Of note, Hatzelmann and associates[33] showed that, whereas **theophylline inhibits complement** component C5a-stimulated human eosinophil granule release, this effect was **not reproduced** with selective **PDE type IV inhibitors** like rolipram (type IV PDE is the predominant isoenzyme in eosinophils).[33] This implies that PDE inhibition is not the only reason for some of the effects of theophylline on eosinophil function. [Vassallo et al. at page 348, first column, emphasis added]

Thus, Vassallo et al. teaches that theophylline also shows effects that must be explained by reasons other than PDE inhibition. These teachings must all be kept in line because it is only after reading such teachings that one gets to the discussion of theophylline inducing apoptosis in CLL cells. Vassallo et al. specifically states after discussing this that "the **mechanism** by which theophylline induces apoptosis **is unclear**. PDE inhibition and intracellular cAMP accumulation **may** have a role." Such a statement implicitly teaches that PDE inhibition may also not have a role. Accordingly, the skilled artisan reading Vassallo et al. is told that it has been observed that theophylline can induce apoptosis in CLL cells. However, the basis by which theophylline is causing such apoptosis is explicitly disclosed as being unknown. It might be a result of PDE inhibition, but even if it was believed that PDE inhibition played a role, there is nothing in this article that suggests that it is type IV inhibition as opposed to type I, II, VII or any other. It is taught in this article that theophylline and PDE type IV inhibitors can show different effects (see, page 348 discussed above). It was in no way clear that theophylline functioned like a PDE

inhibitor, and in particular whether it acted as a PDE4 inhibitor, when it displayed anti-CLL activity. Mentz et al. further shows that even in 1999, the mechanism by which theophylline induces apoptosis in CLL cells is unknown (see, Exhibit 1, Mentz et al.; Leukemia; 13:78-84 (1999) at page 80). There are mechanisms other than increasing cAMP in CLL cells that can increase apoptosis. Thus, it would not have been obvious that a PDE4 inhibitor would work as is herein taught.

In fact, Applicant shows in Example 3 and Figure 4D that vinpocetine, a PDE1 inhibitor, has a significantly different effect on cAMP induction in CLL cells than rolipram, a PDE4 inhibitor. Thus, there is nothing in Vassallo et al. that would in any way render it obvious that using a type IV specific inhibitor as explicitly claimed herein would have any effect on CLL. Indeed, the present application in Figures 12A, 12B and 14 show that in direct comparisons the compared PDE4 inhibitors work better than theophylline.

Accordingly, Applicant respectfully submits that Vassallo et al. does not render the present invention obvious. It does not suggest the use of a PDE4 inhibitor any more than a PDE1 inhibitor, nor does it even suggest that any PDE inhibitor would be effective against CLL. Accordingly, this rejection should be withdrawn.

In view of the foregoing, Applicant respectfully submits that all claims are in condition for allowance. Early and favorable action is requested.

In the event that any additional fees are required, the PTO is authorized to charge our Deposit Account No. 50-0850.

Respectfully submitted,

Date: October 25, 2005

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